Congenital Toxoplasmosis With Hemolytic Anemia

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AN INFANT WITH congenital toxoplasmosis of the visceral type, who had hepatosplenomegaly and jaundice when first examined, was cared for at the Premature Center of the Los Angeles County Hospital. The infant had an isolated episode of acute hemolytic anemia, which is an unusual finding in this disease.

Case Report

The patient was born of a 26-year-old gravida 4 para 3 Mexican-American woman following 36 weeks of gestation. The mother had no prenatal care and had taken no medicines during this pregnancy. The only illness was a "bad cold" of four days' duration at five months of gestation. No fever, rash or lymphadenopathy was recalled during this illness. At the time of the mother's illness, the patient's father, age 28 years, was also ill with high fever and malaise. He made an uneventful recovery and had no medical care. The three normal siblings aged five, four, and three years were not ill at that time.

The delivery of this infant, a girl, was in a physician's office after a spontaneous labor. The amniotic fluid was described as "foul smelling." The infant was admitted first to another hospital and was transferred to the Premature Center of the Los Angeles County Hospital at two days of age.

On admission the infant weighed 1,960 gm. She had both jaundice and hepatosplenomegaly. Hemoglobin content was of 18 gm per 100 ml of blood, and urinalysis was within normal limits. The total bilirubin concentration was 9.6 mg per 100 ml and the serologic test for syphilis (VDRL) was negative. An x-ray film of the chest showed no abnormality but enlargement of the liver and spleen was apparent on a radiograph of the abdomen. A blood culture showed no growth. No cytomegalic inclusion cells were found in the urine on repeated examination.

Bilirubin levels during the following 20 days are shown in Table 1. These showed persistent high levels of the direct-reacting bilirubin fraction. At 20 days of age, liver function tests included albumin of 4.0 gm and globulin of 2.9 gm per 100 ml and a serum glutamicoxaloacetic transaminase of 225 units. The hemoglobin level at that time was 9.9 gm per 100 ml.

Both the patient's and the mother's blood types

TABLE 1.—*Serial Bilirubin Determinations in Infant with Congenital Toxoplasmosis*

Age (days)	*Bilirubin (mg per cent)*	
	Total	*Direct*
2	9.6	....
3	9.0	4.6
4	8.0	4.2
20	5.2	2.6
22	5.1	2.8

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were group A, Rh positive. Reaction to a Coombs test on the patient's blood was negative. Seven days later the hemoglobin had dropped to 6.8 gm per 100 ml, the packed cell volume was 20 per cent, and the total leukocyte count was 4,500 per cu mm with a normal differential. The platelets appeared slightly reduced in number on a peripheral smear. Two normoblasts were seen per 100 leukocytes. The reticulocyte count was 3.4 per cent when corrected for anemia. The erythrocytes were normochromic and the mean corpuscular hemoglobin concentration was 34 per cent. Microcytes and some spherocytes were present. A sickle cell preparation was negative. An erythrocyte glucose-6-phosphate dehydrogenase spot test was within normal limits.

A transfusion of 20 ml of sedimented red blood cells was given on the twenty-seventh day. Active erythropoesis was seen on bone marrow aspiration at 37 days of age. The myeloid series was within normal limits and no abnormal cells were seen. A percutaneous liver biopsy done at 32 days of age showed extramedullary hematopoesis with conspicuous hemosiderosis consistent with a hemolytic process. After the transfusion and until the time of discharge, the hemoglobin level stabilized between 8.5 and 9.6 gm per 100 ml.

At 20 days of age, no red or light reflex could be elicited in the right eye. The cornea was clear, the pupil did not dilate well, and posterior synechiae were present. The fundus could not be seen adequately. The left cornea was clear and the pupil dilated well. The fundus was easily visualized and no abnormalities were present.

In the nursery the baby was vigorous and had regained her admission weight by the tenth day. She was asymptomatic during her entire stay in hospital. No therapy other than a routine multiple vitamin preparation was given in the nursery. The infant was discharged from the hospital at 46 days of age weighing 2,850 gm and with equivocal clinical jaundice and persistent hepatosplenomegaly.

She was observed in the outpatient department until twenty-two and a half months of age. Weight gain was from 4,252 gm at five months to 8,796 gm at 11 months (both in the twenty-fifth percentile).[16] Head circumference at 11 months was 43 cm (third percentile).[16] At five months of age hepatosplenomegaly was present without jaundice. A Sabin-Feldman dye test was positive at 1:64,000 (Table 2). X-ray films of the skull showed no abnormality. Ophthalmoscopic examination after sedation indicated both micro-opthalmia and iritis of the right eye. Again the fundus could not be visualized. Both vitreous haze and chorioretinitis were present in the left eye. Internal strabismus of the right eye and wandering eye motions had developed by 11 months of age and persisted thereafter.

TABLE 2.—*Sabin-Feldman Dye Titers in a Case of Congenital Toxoplasmosis*

Age (months)	*Patient*	*Mother*
5	1:64,000	1:64,000
11	1:32,000	1:64,000
22	1:16,000	1:64,000

The hemoglobin rose from 9.0 gm per 100 ml at five months of age to 12.2 gm at 11 months. Results of the repeated Sabin-Feldman dye tests and complement fixation tests for toxoplasmosis for both the patient and her mother are tabulated in Table 2. At 11 months of age, pyrimethamine, 12.5 mg per day and sulfisoxasole 150 mg per kg of body weight per day, were begun and continued for 30 days with no change in the patient's condition.

Gesell developmental testing done at the chronological age of twenty-two and a half months gave the following results: Motor 17 to 18 months, adaptive 16 months, language 15 months, and social-personal 15 to 16 months. Despite the obvious visual difficulties, she was able to secure the pellet against a white background, establishing that poor vision was not the only cause for her delayed development. Her adaptive behavior at a 16-month level would seem to be the most accurate appraisal of her development at this time.*

The mother was admitted to hospital seven months after birth of the patient for an incomplete abortion. Curettement of the uterus was performed, and on examination of the tissue removed at curettage no toxoplasma was observed.

Discussion

Since the recognition of the first cases of congenital toxoplasmosis published in 1939,[18] a concept has persisted that the disease presents as a parasitic central nervous system infection with hydrocephalus or microcephalus, convulsions, intracerebral calcification, chorioretinitis and mental retardation. In one of the early reports, the symp-

*Developmental testing done by Anabel Teberg, M.D., assistant clinical professor of pediatrics, University of Southern California.

toms first observed were referable to the viscera.[8] In 1956, Eichenwald[9] reported a series of 156 cases of congenital toxoplasmosis. One hundred and eight of the patients had central nervous system abnormalities whereas 44 patients had predominately visceral findings. In the latter group, jaundice was present in 79 per cent of cases, anemia in 77 per cent, chorioretinitis in 66 per cent and splenomegaly in 90 per cent. Intracranial calcifications were found in only 4.5 per cent of this group, and hydrocephalus in none. Couvreur and Desmonts,[7] in a series of 300 cases of congenital toxoplasmosis reported from France, found neurological disorders in 51 per cent, hydrocephaly or microcephaly in 26 per cent, ocular disorders in 76 per cent, intracranial calcifications in 33 per cent, jaundice in 20 per cent and hepatosplenomegaly in 18 per cent. Other smaller series have shown a preponderance of patients with central nervous system disease and a smaller proportion with visceral manifestations.[1,4,6,15] In cases of congenital toxoplasmosis in which the early symptoms were related primarily to visceral infections, the central nervous system was ultimately affected to a greater or lesser degree.[9]

Jaundice is common in the visceral form of the disease, but examples of well documented cases of elevated direct-reading bilirubin are uncommon in the literature.[5] Cowen and coworkers[8] described a case of congenital toxoplasmosis in which total bilirubin when the patient was nine days old was 15.3 mg per 100 ml, of which 8.5 mg per 100 ml was direct reacting. At 30 days of age the same infant had total bilirubin of 5.8 mg per 100 ml with a direct bilirubin of 3.7 mg per 100 ml. Another patient had well documented direct hyperbilirubinemia of 12 mg per 100 ml on the first day of life. Elevated direct bilirubin has been reported in only two additional cases.[15,19] A direct bilirubin level over 1 mg per 100 ml is an unusual finding in the newborn,[12] and when it is increased, congenital toxoplasmosis should be considered in differential diagnosis.

Several cases have been reported in which infants at birth who died of anemia resembling hemolytic disease of the newborn, were found at necropsy to have congenital toxoplasmosis with no apparent blood incompatibility.[2,3,5] Few cases have been reported in which infants who had anemia with congenital toxoplasmosis survived.[8,11,19] The case herein reported, in which anemia was noted when the infant was 27 days old, is a well documented instance of hemolysis which must be considered as a part of the visceral manifestations of congenital toxoplasmosis.

The benefit of treatment in congenital toxoplasmosis is questionable. Although both sulfonamides and pyrimethamine are active against toxoplasma *in vitro,* the results *in vivo* have been equivocal.[20] Eichenwald found that in a small group of infants treatment appeared to shorten the acute phase of the illness, and reversion of dye test titers to lower levels also occurred. Treatment does not appear to prevent the neurologic sequelae of neonatal infection.

The prognosis in congenital toxoplasmosis remains poor. The mortality in a group of 103 cases reported by Feldman[10] was 27 per cent in premature infants and 12 per cent in term infants. In Eichenwald's[9] study of 156 cases the overall mortality was 12 per cent. Of the surviving infants, 90 per cent had mental retardation, 70 per cent had convulsions, spasticity or other neurologic abnormalities and 50 per cent had severely impaired vision. Chorioretinitis may not be present at birth, particularly in the visceral group, but it may develop, as in the present case, from two weeks to six months later.[7,13,17]

Summary

Congenital toxoplasmosis in a premature infant first came to attention because of visceral manifestations of jaundice and hepatosplenomegaly at two days of age. Direct hyperbilirubinemia persisted for 46 days and an isolated episode of acute hemolytic anemia occurred at 27 days of age. Ocular changes were first noted at 20 days of age. The diagnosis was confirmed by demonstrating persistently elevated Sabin-Feldman dye test titers in both mother and infant.

At twenty-two and a half months of age the infant was growing normally but with severe visual impairment and developmental retardation.

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Necrotic Arachnidism

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NOT OFTEN DO humans die of spider bite, but a more frequent if less appreciated consequence is cutaneous necrosis at the site of venom injections. The lesions are so fulminant and ugly-appearing that it is difficult to associate them with anything as small as a spider and they are therefore often mistakenly attributed to other causes.

As a case in point, a patient was admitted to our service with extensive necrotic ulcerations on the foot and buttocks. The history was highly suggestive of an insect bite, but there was no known organism in California that was reported capable of producing so astounding a lesion. However, careful review of medical and zoological literature elicited reports of an arachnid, the *Loxosceles spider*—only endemic in certain midwestern states—whose bite did cause necrotic lesions. There was a most remarkable similarity between history and clinical manifestations in the present case and the necrotic arachnidism reported caused by this midwestern species.

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Etiology and Epidemiology

Necrotic arachnidism (cutaneous necrosis following spider bite) has been known to physicians of South America for many years. Although Prada in 1896 reported the first case of gangrenocutaneous arachnidism in South America resulting from the bite of a small brown spider, it was not until 1937 that Macchiaviello identified the spider *Loxosceles laeta* as the causative agent of Chilean cutaneous arachnidism—"gangrenous spot." Numerous papers, especially from the University of Chile, have subsequently reported upon the incidence of necrotic arachnidism and on its treatment.

In the United States, reports of identical or very similar cases of necrotic arachnidism (caused by some unknown insect or spider) have frequently appeared in the literature. These date back to as early as 1890, when an article appearing in a local journal of medicine in Missouri reported a case of necrotic arachnidism resulting from the bite of a small spider, the species not known.

Until less than a decade ago, *Lactrodectus mactans* (the Black Widow spider) was the only culprit within the United States known to cause necrotic arachnidism. Then, in 1957, the Missouri Brown spider, *Loxosceles reclusa*,[1] was proved to be capable of causing such lesions. Clinically, the lesion produced by the bite of this spider is one of central necrosis—completely unlike that produced by the black widow, which rarely causes necrosis, but similar to the necrotic, cutaneous ulcerations produced by its South American relative, *Loxosceles laeta*.

Interestingly, the geographic incidence of the